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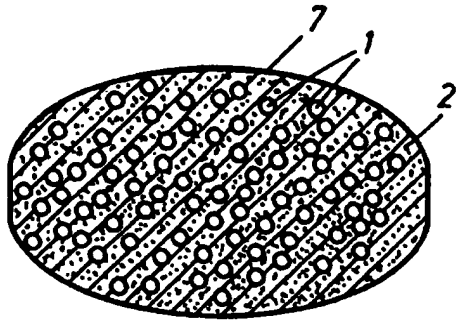
(54) Title: ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND AN ANTACID AGENT OR ALGINATE

(57) Abstract

An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor and one or more antacid agents or an alginate in a fixed formulation, wherein the proton pump inhibitor is protected by an enteric coating layer and an optional separating layer in between the proton pump inhibitor and the enteric coating. The fixed formulation is in the form of multilayered tablets, sachets or multiple unit tableted dosage forms. The multiple unit dosage form is most preferred. The new fixed formulation is especially useful in the treatment of disorders associated with dyspepsia such as heartburn.



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ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND AN ANTACID AGENT OR ALGINATE

Field of the invention

The present invention is related to new oral pharmaceutical preparations especially for use in the prevention and treatment of dyspeptic symptoms like upper abdominal pain/discomfort and heartburn. The present preparations comprise a combination of different gastric acid suppressing agents, such as an acid susceptible proton pump inhibitor and antacid agent(s) and /or an alginate in a new fixed unit dosage form, especially a tableted dosage form. Furthermore, the present invention refers to a method for the manufacture of such preparations and the use of such preparations in medicine, especially in the treatment of dyspeptic symtoms.

Background of the invention

Dyspepsia is a common disorders and patients are seeing both gastroenterologists and general practicians because of it. Heartburn is a symptom of dyspepsia, and it is estimated that 44% of Americans have heartburn at least monthly and some has to contact a doctor about the problem, but only around 25 % of the patients are seeing the doctor because of their dyspepsia problem. Symtoms associated with dyspepsia symtom are for instance upper abdominal pain/discomform and heartburn, indigestion, sour stomach, heartburn and other gastrointestinal disorders including gastro oesophageal reflux.The wide diversity of symptoms and disease severity produced by gastro oesophageal reflux has led to the need for more individualized treatment strategies.

Therapeutic agents effective in the treatment of dyspepsia include gastric acid suppressing agents, such as H_2 receptor antagonists, proton pump inhibitors, other agents of interest are antacids/alginates and prokinetic agents. These agents can be distinguished by their mechanisms of action, safety profile, pharmacokinetics and indications.

WO 95/017080 describes a composition for use in the treatment of for instance heartburn, the composition comprises a H_2 receptor antagonist, such as famotidine, and an alginate and optionally simethicone.

Antacid agents and alginates may be used alone in the treatment of heartburn. They have a short duration of action but are seen as inexpensive and safe. Antacid agents work locally through a neutralisation of gastric acid. Alginates further give some mechanical protection against reflux or gastric acid into the oesophagasus. The main advantages of antacid agents and alginates are, that they provide fast relief of symtoms. The main disadvantage of antacid agents and alginates is that, dosing has to be repeated frequently to keep the patients free of symtoms, further that antacids in many cases do not provide symtom resolution, i.e. complete relief of symtoms.

H_2 receptor antagonists are widely prescribed for reducing gastric acid secretion systemically. Proton pump inhibitors, such as omeprazole, are rapidly taking share from H_2 receptor antagonists. Omeprazole is known to offer significant gain over H_2 receptor antagonists in terms of symptom resolution, healing and prevention of relapse. Proton pump inhibitors provide symtom resolution, but normally not immediately.

Proton pump inhibitors have in clinical studies been proven to be very effective in providing symtom resolution (usually within 24 - 48 hours) in patients with dyspepsia associated with gastric ulcers, duodenal ulcers, reflux oesophagitis and gastro oesophageal reflux without oesophagitis. It is for instance established that omeprazole is superior to H_2 receptor antagonists regarding healing of gastroduodenal and oesophageal lesions as well as providing dyspeptic symtom resolution in these conditions, See Eriksson S., Euro Journ of Gastroenterology & Hepatology 1995, 7 : 465.

EP 338861 describes a solid pharmaceutical preparation of an antacid and excipients. It is proposed to use this preparation in combination with a proton pump inhibitor or any other

substance inhibit gastric acid secretion. There is no suggestion to combine these substances in one fixed unit dosage form.

US 5 244 670 describes an ingestible pharmaceutical composition comprising a substance selected from the group consisting of antacid agents, acid secretion prevention agents, bismuth-containing agents, and mixtures thereof, and the excipient 3-1-menthoxy propane 1,2-diol. There are no specific arrangements discussed in neither of these references, to solve the problem with one of the component being an acid susceptible proton pump inhibitor.

A combination therapy of a proton pump inhibitor and an antacid or an alginate would provide immediate symtom relief, provided by the local effect of the antacid agent or the alginate, combined with a long-lasting symtom resolution provided by the systemically acting proton pump inhibitor. Such a combination would be ideal for "on-demand treatment " of dyspepsia as well as for symtom resolution. The combination therapy comprising an acid suppressing agent, for instance a proton pump inhibitor, together with an antacid agent or an alginate could also be an alternative to each of them separately in case of failure.

It is well known that patient compliance is a main factor in receiving good results in medical treatments. Administration of two or even more different tablets to the patient is not convenient or satisfactory to achieve the most optimal results. The present invention now provides new oral dosage forms comprising two or more active substances combined in one fixed unit dosage form, preferably a tablet.

Some gastric acid suppressing agents, such as proton pump inhibitors, are susceptible to degradation/transformation in acid reacting and neutral media. In respect of the stability properties, it is obvious that the one of the active substances being a proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of proton pump inhibitors described in the

prior art, see for example US-A 4,786,505 (AB Hässle) describing a preparation comprising omeprazole.

There are problems to produce a fixed unit dosage form comprising a rather high amount of active substance. Different active substances in the same preparation give further problems. Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets comprising an acid susceptible proton pump inhibitor as active substance are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be destroyed upon administration by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

Summary of the invention

The present invention provides oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, layered formulations comprising an enteric coating layered tablet core, multilayered tablets or a sachet filled with more than one pharmaceutically active compound. The active compounds present in the dosage form are preferably an acid susceptible proton pump inhibitor and antacid agents. Alternatively, in some of the formulations the antacid agents may be replaced by an alginate. These new dosage forms will simplify the regimen and improve the patient compliance.

Brief description of the Figures

Fig. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with antacid agent(s) and pharmaceutical excipients(2). Optionally, the tablet is covered by a filmcoating layer, i.e. tablet coat (7).

Fig. 2 illustrates a cross-section of a tablet with two separate layers, one of which comprising enteric coating layered pellets of an acid susceptible proton pump inhibitor (1) in admixture with excipients (3) and the other layer comprising a mixture of pharmaceutical excipients and an antacid agent(s) or an alginate (2). Optionally the layers are separated by an anti-tacking layer. Further the tablet is optionally covered by a filmcoating layer (7).

Fig. 3 illustrates a cross-section of a tablet comprising a mixture of pharmaceutical excipients and an acid susceptible proton pump inhibitor in the tablet core (5) surrounded by of an enteric coating layer (8) optionally with a separating layer applied in between the tablet core and the enteric coating layer and upon the enteric coating layer a layer of the antacid agent(s) in admixture with pharmaceutical excipients 6). Optionally, the tablet is covered by a filmcoating layer (7).

Detailed description of the invention

One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of individually enteric coating layered units together with one or more antacid agents in the form of a powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible proton pump inhibitor has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units. Furthermore, the multiple unit tableted dosage form provides a good stability to the active substances during long-term storage.

A further object of the invention is to provide a multiple unit tableted dosage form, which is divisible and easy to handle. Such a multiple unit tableted dosage form comprising enteric coating layered pellets of a proton pump inhibitor and antacid agent(s) also may be dispersed in a slightly acidic aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed units/pellets of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

Another object of the invention is to provide a tablet preparation comprising a proton pump inhibitor in admixture with tablet excipients in a tablet core and a separate layer surrounding the tablet core, which layer comprises one or more antacid agent(s) in admixture with pharmaceutical excipients compressed onto the tablet core. The tablet core is enteric coating layered before the surrounding layer comprising the antacid agents is applied. Optionally a separating layer is applied on the tablet core before the core is enteric coating layered.

Alternatively, the prepared tablet is sectioned in separate layers, each one comprising different active substances. One of the layers comprises the proton pump inhibitor in the form of enteric coating layered pellets in admixture with pharmaceutical excipients and the other layer(s) comprises(-e) the antacid agent(s)/alginate, respectively in admixture with pharmaceutical excipients. Optionally the two layers are separated by a separating layer to prevent tacking between the two layers.

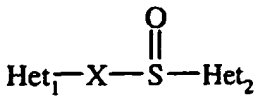
The new fixed unit dosage forms comprise as active substances one gastric acid suppressing agent, such as an acid susceptible proton pump inhibitor, and antacid agent(s)/alginate. Alternatively, the proton pump inhibitor in the form of enteric coating layered pellets may be mixed with an alginate and optionally pharmaceutical excipients to be administred in a sachet intended for oral administration after dispersion in a sligthly acidic aqueous solution. The new fixed dosage form is preferably in the form of a multiple unit tableted dosage form containing enteric coating layered units comprising the active substance being an acid susceptible proton pump inhibitor and granules comprising the other active substance(s), i.e. the antacid agent(s) as shown in Fig. 1.

The antacid agent(s) may preferably be formulated in preparations intended for instant release. Alternatively, the components may be formulated in an effervescent formulation.

The different therapeutically active components used in the dosage forms are defined below.

Active substances

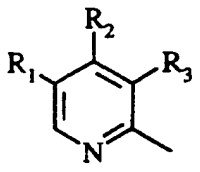
The gastric acid suppressing agent is preferably an acid susceptible proton pump inhibitor. Such proton pump inhibitors are for example compounds of the general formula I



I

wherein

Het_1 is



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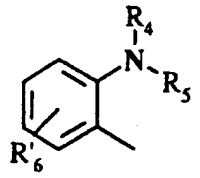

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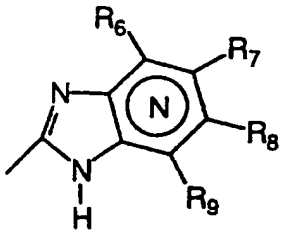

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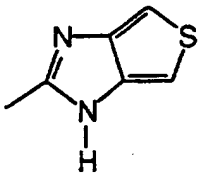

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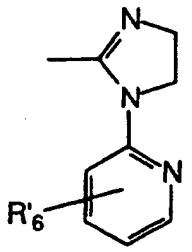
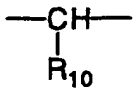


X =



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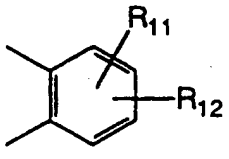


wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

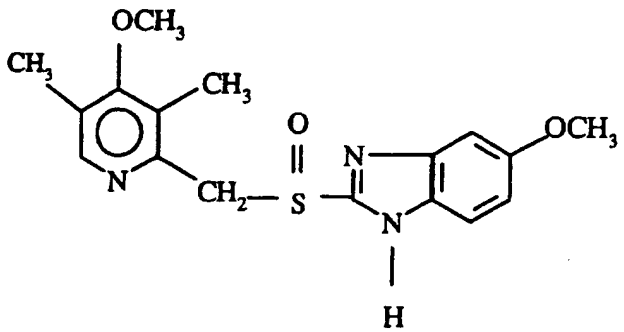
R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;
R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

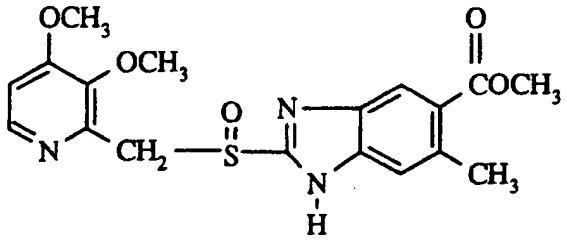
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

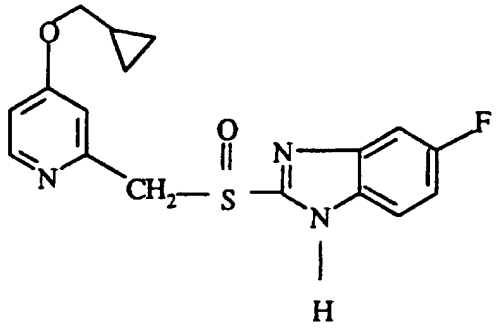
R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C_1 - C_9 - chains or comprise cyclic alkyl groups, such as cycloalkylalkyl.

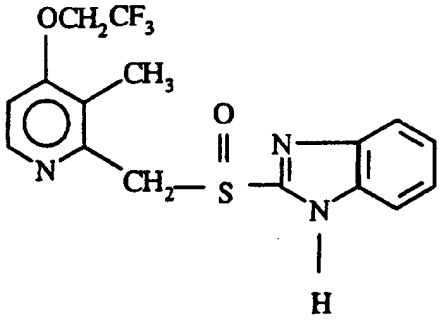
Examples of proton pump inhibitors according to formula I are



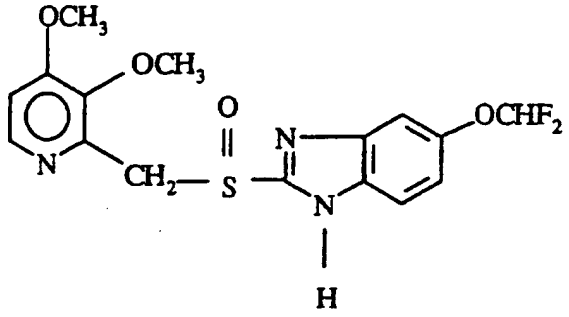
Omeprazole



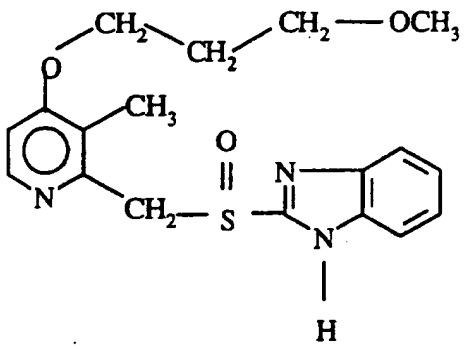




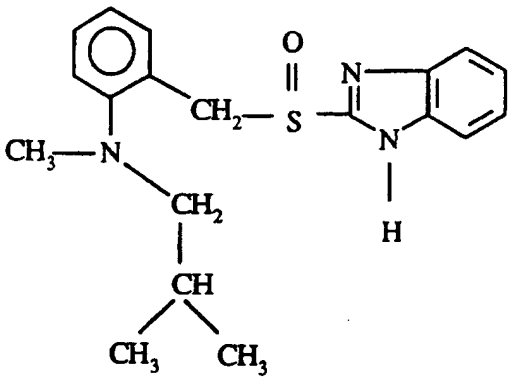
Lansoprazole



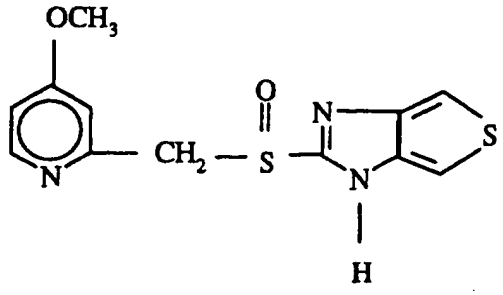
Pantoprazole

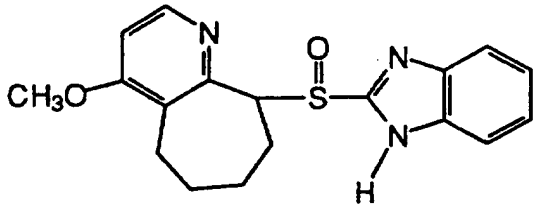


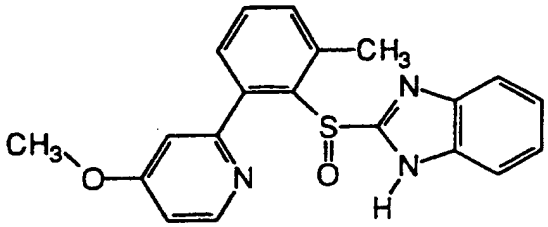
Pariprazole

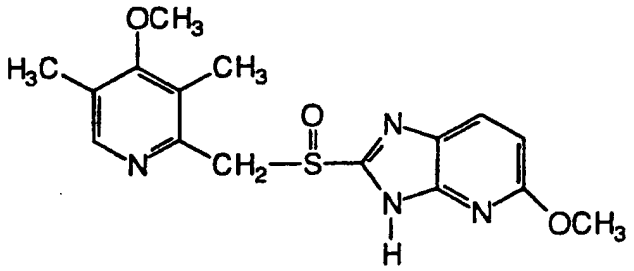


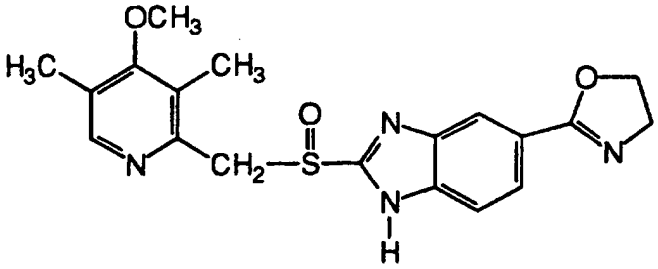
Leminoprazole











The proton pump inhibitors used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+}, Ca^{2+}, Na^{+}, K^{+} or Li^{+} salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO95/01977 and WO94/27988.

The gastric acid suppressing agent is preferably an acid susceptible proton pump inhibitor but H_2 receptor antagonists such as ranitidine, cimetidine or famotidine may be used in the pharmaceutical compositions with an alginate as proposed in WO 95/ 017080 or together with antacid agent(s).

A wide variety of antacid agent(s) and/or alginates may be used in combination with a suitable proton pump inhibitor in the fixed unit dosage form according to the present invention. Such antacid agents include for example aluminium hydroxide, calcium carbonate, magnesium hydroxide, magnesium carbonate and aluminium magnesium hydroxide carbonate (hydrotalcit) taken alone or in combinations with each other. The alginates may be an alginate selected from alginic acid or sodium alginate or other pharmaceutically acceptable alginate salts, hydrates, esters etc. Especially preferred antacid agents are magnesium or calcium based antacid agents and aluminium hydroxide/magnesium carbonate complex. Suitable antacid agents are for instance described in US 5 409 709.

The preferred multiple unit tableted dosage form comprising a proton pump inhibitor in the form of a racemat, an alkaline salt or one of its single enantiomers in combination with antacid agent(s), is characterized in the following way. Individually enteric coating layered units (small beads, granules or pellets) containing the acid susceptible proton pump inhibitor and optionally containing alkaline reacting substances, are mixed with the antacid(s) and conventionally tablet excipients. The antacid(s) and tablet excipients may be dry mixed or wet-mixed into granules. The mixture of enteric coating layered units, antacid agent(s) and optionally excipients are compressed into the multiple unit tableted dosage forms. With the

expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the proton pump inhibitor.

The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric coating layer(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid resistance does not decrease more than 10% during the compression of the pellets into tablets.

The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0,1 M HCl (aq) relative to that of unexposed tablets and pellets, respectively. The test is accomplished in the following way. Individual tablets or pellets are exposed to simulated gastric fluid of a temperature of 37°C. The tablets disintegrate rapidly and release the enteric coating layered pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid Chromatography (HPLC).

Further specific components used in the fixed unit dosage forms of the present invention are defined below.

Core material - for enteric coating layered pellets comprising a proton pump inhibitor

The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

The seeds which are to be layered with the proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or

in mixtures or water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

Before the seeds are layered, the proton pump inhibitor may be mixed with further components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl-cellulose (HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into a core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing conventional process equipment. The size of the formulated core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

The proton pump inhibitor is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives.

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethyl-aminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

Enteric coating layer(s)

Before applying the enteric coating layer(s) onto the core material in the form of individual pellets or tablets, the pellets or tablets may optionally be covered with one or more separating layer(s) comprising pharmaceutical excipients optionally including alkaline compounds such as pH-buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s). The separating layer(s) protecting the proton pump inhibitor should be water soluble or rapidly disintegrating in water.

The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for the separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl

acetate, hydroxypropyl cellulose, methylcellulose, ethyl-cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the separating layer(s).

When the optional separating layer, is applied to the core material it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other compounds may be added to increase the thickness of the layer(s) and thereby strenghten the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.

Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in the position to form a salt.

The separating layer may also be used to separate two different layers of a tablet, as described in Fig. 2.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents.As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments polymers e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 µm, preferably more than 20 µm. The maximum thickness of the applied enteric coating is normally limited by processing conditions and the desired dissolution profile.

Alternatively, the enteric coating layer described above may also be used for enteric coating of conventional tablets comprising an acid susceptible proton pump inhibitor. Said enteric coating layered tablet is thereafter presscoated with antacid granules and pharmaceutical excipients.

Over-coating layer

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) should be water soluble or rapidly disintegrating in water. The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such for instance magnesium stearate, titaniumdioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, further protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally limited by processing conditions and the desired dissolution profile.

The above described over-coating layer may also be used as a tablet filmcoating layer to obtain tablets of good appearance.

Antacid agent(s) or alginate preparation

The active substance in form of one or more antacid agent(s) are dry mixed with inactive excipients such as fillers, binders, disintegrants, and other pharmaceutically acceptable additives.The mixture is wet massed with a granulation liquid. The wet mass is dried preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for the granules, such as smaller than 4 mm, and preferably smaller than 1 mm. Suitable inactive excipients are for instance mannitol, corn starch, potato starch, low substituted hydroxypropylcellulose, microcrystalline cellulose and crosslinked polyvinylpyrrolidone. The dry mixture comprising antacid agent(s) is mixed with a suitable granulation liquid comprising for instance hydroxypropylcellulose or polyvinylpyrrolidone dissolved in purified water or alcohol or a mixture thereof.

Alternatively, the antacid agent(s) are dry mixed with pharmaceutically acceptable excipients according to the above. The alginate preparation should also be prepared by dry mixing with pharmaceutically acceptable excipients.

Multiple unit tablets

The enteric coating layered pellets comprising a proton pump inhibitor are mixed with the prepared antacid granules or with the prepared dry mixture comprising the antacid agent(s). The mixture is admixed with lubricant(s) and compressed into a multiple unit tableted dosage form. Suitable lubricants for the tableting process are for instance sodium stearyl fumarate, magnesium stearate and talc.The compressed tablet is optionally covered with a filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a coating layer may further

comprise additives such as anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

Further, the different active substances may be formulated into different layers, wherein the layer comprising the proton pump inhibitor preferably is in the form of a multiple unit tableted dosage form layered with the prepared mixture of the antacid agent(s) or an alginate preparation. The two layers may be separated by a third layer comprising anti-tacking agents.

The fraction of enteric coating layered pellets constitutes less than 75 % by weight of the total tablet weight and preferably less than 60 %. By increasing the amount of the granules comprising the antacid agent(s) and excipients, the fraction of enteric coating layered pellets of the proton pump inhibitor may be reduced in the multiple unit tableted dosage form. By choosing small enteric coating layered pellets in the formulation according to the present invention, the number of pellets in each tablet can be held high which in turn makes the tablet divisible with retained dosing accuracy.

Thus, the preferred multiple unit tablet formulation consists of enteric coating layered pellets containing the acid susceptible proton pump inhibitor, optionally in admixture with alkaline reacting compound(s), compressed into tablets together with the prepared antacid mixture and optionally tablet excipients. The addition of an alkaline reacting material to the proton pump inhibitor is not necessary, in any sense, but such a substance may further enhance the stability of the proton pump inhibitor or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating layer. The enteric coating layer(s) is making the pellets of the dosage form insoluble in acidic media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the proton pump inhibitor is desired. The enteric coating layered pellets may further be covered with an overcoating layer before being formulated into the tablet and they may also contain

one or more separating layer(s) in between the core material and the enteric coating layer(s).

Process

The process for the manufacture of the dosage form represents a further aspect of the invention. After formulation of the pellets by spray coating or layering of the proton pump inhibitor onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with the separating layer(s) and then with the enteric coating layer(s) or a separating layer is spontaneously developed in situ between the core material and the enteric coating layer material. The coating is carried out as described above and in the accompanying examples. The preparation of the antacid mixture is also described above and in the examples. The pharmaceutical processes can preferably be completely water-based.

The enteric coating layered pellets, with or without an over-coat, are mixed with the prepared antacid granules, tablet excipients and other pharmaceutically acceptable additives and compressed into tablets. Alternatively, the enteric coating layered pellets may be intimately mixed with tablet excipients and precompressed and further layered with the antacid or alginate preparation and finally compressed into a tablet. As a further alternative the proton pump inhibitor in form of a powder may be mixed with tablet excipients and compressed into a tablet which is optionally layered with a separating layer and thereafter enteric coating layered. Said tablet core is then presscoated with the antacid preparation. Finally the tablet may be covered by a tablet coat.

As a further alternative, the proton pump inhibitor in the form of enteric coating layered pellets may be filled in a sachet together with an alginate optionally mixed with excipients.

Use of the preparation

The dosage forms according to the invention are especially advantageous in the treatment of dyspepsia and other gastrointestinal disorder to provide an immidiate symtom relief and a long-lasting symtom resolution. The dosage forms are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0.1-200 mg of the proton pump inhibitor and 0.1-1000 mg of the antacid agent(s)/alginate. Preferably, each dosage form will comprise 5-80 mg of the proton pump inhibitor and 100-900 mg of the antacid agent(s)/alginate, and more preferably 10-40 mg of proton pump inhibitor and 250 - 650 mg of the antacid agent(s)/alginate, respectively.

The multiple unit tablet preparation is also suitable for dispersion in an aqueous liquid with slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

The invention is illustrated more in detail in the following examples.

Examples

Example 1:

Multiple unit tableted dosage form comprising magnesium omeprazole and antacid agents (batch size 400 tablets).

Core material

Magnesium omeprazole	5.0	kg
Sugar sphere seeds	10.0	kg
Hydroxypropyl methylcellulose	0.75	kg
Water purified	20.7	kg

Separating layer		
Core material (acc. to above)	10.2	kg
Hydroxypropyl cellulose	1.02	kg
Talc	1.75	kg
Magnesium stearate	0.146	kg
Water purified	21.4	kg
Enteric coating layer		
Pellets covered with separating layer (acc. to above)	11.9	kg
Methacrylic acid copolymer (30 % suspension)	19.8	kg
Triethyl citrate	1.79	kg
Mono- and diglycerides (NF)	0.297	kg
Polysorbate 80	0.03	kg
Water purified	11.64	kg
Over-coating layer		
Enteric coating layered pellets (acc. to above)	20.0	kg
Hydroxypropyl methylcellulose	0.238	kg
Magnesium stearate	0.007	kg
Water purified	6.56	kg
Tablets		
Prepared pellets comprising omeprazole Mg-salt (acc. to above)	31.3	g
Microcrystalline cellulose	140.0	g
Calcium carbonate	100.0	g
Aluminium hydroxide/magnesium carbonate	100.0	g
Potato starch	46.4	g
Water purified	314	g
Polyvidone crosslinked	38.0	g
Sodium stearyl fumarate	4.6	g

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The size of sugar sphere seeds were in the range of 0.25 to 0.35 mm.

The prepared core material was covered with a separating layer of a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. In a fluid bed apparatus enteric coating layered pellets were coated with a hydroxypropyl methylcellulose containing magnesium stearate. The over-coating layered pellets were classified by sieving.

A small amount of the potato starch was dissolved in purified hot water to form the granulation liquid. Calcium carbonate, aluminium hydroxide/magnesium carbonate, potato starch and microcrystalline cellulose are dry-mixed. The granulation liquid was added to the dry mixture and the mass was wet-mixed. The wet mass was dried in a steamoven at 50°C. The prepared granulation was milled through sieve 1 mm in an oscillating mill equipment.

The enteric coating layered pellets with an over-coating layer, prepared granules, polyvidone crosslinked and sodium stearyl fumarate were mixed and compressed into tablets using a tableting machine equipped with 9x20 mm oval punches. The amount of omeprazole in each tablet was approx. 10 mg and the amount of antacid agents were approx. 500 mg in total. Tablet hardness was measured to 110N.

Optionally the obtained tablets were covered with a tablet coating layer.

Results

"Acid resistance" i.e. % left after exposure to 0.1 N HCl for 2 hrs	
	Tablets
Ex 1	93%

Example 2:

Multiple unit tableted dosage form comprising magnesium omeprazole and antacid agents (batch size 500 tablets).

Core material

Magnesium omeprazole	10.0 kg
Sugar sphere seeds	10.0 kg
Hydroxypropyl methylcellulose	1.5 kg
Water purified	29.9 kg

Separating layer

Core material (acc. to above)	20.0 kg
Hydroxypropyl cellulose	2.0 kg
Talc	3.43 kg
Magnesium stearate	0.287 kg
Water purified	41.0 kg

Enteric coating layer

Pellets covered with separating layer (acc. to above)	24.5 kg

Methacrylic acid copolymer (30 % suspension)	32.7 kg
Triethyl citrate	2.94 kg
Mono- and diglycerides (NF)	0.49 kg
Polysorbate 80	0.049 kg
Water purified	19.19 kg

Over-coating layer

Enteric coating layered pellets (acc. to above)	37.8 kg
Hydroxypropyl methylcellulose	0.49 kg
Magnesium stearate	0.0245 kg
Water purified	11.6 kg

Tablets

Prepared pellets comprising magnesium omeprazole (acc. to above)	47.45 g
Calcium carbonate	123.9 g
Magnesium hydroxide	123.9 g
Potato starch	52.2 g
Water purified	435 g
Microcrystalline cellulose	175 g
Polyvidone crosslinked	50 g
Sodium stearyl fumarate	6.0 g

Enteric coating layered pellets of magnesium omeprazole with an overcoating layer were prepared as in Example 1.

A small amount of the potato starch was dissolved in hot purified water to form the granulation liquid. Calcium carbonate, magnesium hydroxide and potato starch were dry-mixed. The granulation liquid was added to the dry mixture and the mass was wet-mixed. The wet mass was dried in a steamoven at 40 °C. The prepared granulation was milled through sieve 1 mm in an oscillating mill equipment.

The enteric coated layered pellets with an over-coating layer, prepared granules, microcrystalline cellulose, polyvidone crosslinked and sodium stearyl fumarate were mixed and compressed into tablets using a tableting machine equipped with 9x20 mm oval punches. The amount of omeprazole in each tablet was approx. 20 mg and the amount of antacid agents were approx. 500 mg in total. Tablet hardness was measured to 30-40N.

Optionally the obtained tablets were covered with a tablet coating layer.

Example 3:

Multiple unit tableted dosage form comprising S-omeprazole magnesium salt and antacid agents (batch size 500 tablets).

Core material	
S-omeprazole magnesium salt	120 g
Sugar sphere seeds	150 g
Hydroxypropyl methylcellulose	18 g
Polysorbate 80	2.4 g
Water purified	562 g
Separating layer	
Core material (acc. to above)	200 g
Hydroxypropyl cellulose	30 g
Talc	51.4 g
Magnesium stearate	4.3 g
Water purified	600 g
Enteric coating layer	
Pellets covered with separating layer (acc.to above)	250 g

Methacrylic acid copolymer (30% suspension)	333.7 g
Triethyl citrate	30 g
Mono- and diglycerides (NF)	5 g
Polysorbate 80	0.5 g
Water purified	196 g

Tablets

Prepared pellets comprising (s)-omeprazole Mg-salt	63.7 g
Calcium carbonate	123.9 g
Magnesium hydroxide	123.9 g
Potato starch	52.2 g
Water purified	435 g
Microcrystalline cellulose	175 g
Polyvidone crosslinked	50.0 g
Sodium stearyl fumarate	6.0 g

Suspension layering was performed in a fluid bed apparatus. S-omeprazole magnesium salt was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder and polysorbate 80. The size of sugar sphere seeds were in the range of 0.25 to 0.35 mm.

The prepared core material was covered with a separating layer in a fluid bed apparatus with hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono-and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. The enteric coating layered pellets were classified by sieving.

A small amount of the potato starch was dissolved in hot purified water to form the granulation liquid. Calcium carbonate, magnesium hydroxide and potato starch were dry-mixed. The granulation liquid was added to the dry mixture and the mass was wet-mixed.

The wet mass was dried in a steamoven at 40 °C. The prepared granulation was milled through sieve 1 mm in an oscillating mill equipment.

The enteric coating layered pellets, prepared granules, polyvidone crosslinked, microcrystalline cellulose and sodium stearyl fumarate were mixed and compressed into tablets using a tableting machine equipped with 9x20 mm oval punches. The amount of S-omeprazole in each tablet was approx. 20 mg and the amount of antacid agents were approx. 500 mg in total. Tablet hardness was measured to 30N.

Optionally the obtained tablets were covered with a tablet coating layer.

Exampel 4:

Three-layered tableted dosage form with a fast disintegrating layer comprising omeprazole, a separating layer and a layer comprising alginic acid. (batch size 1 000 tablets)

Tablets

First tablet layer	
Alginic acid	500 g
Sodium hydrogencarbonate	150 g
Microcrystalline cellulose	87 g
Polyvinyl pyrrolidone crosslinked	13 g
Sodium stearyl fumarate	3.8 g
Separating layer	
Microcrystalline cellulose	80 g
Second tablet layer	
Enteric coating layered pellets comprising omeprazole Mg-salt	78.3 g

(manufacturing and composition as in example 1)	
Microcrystalline cellulose	174 g
Polyvinyl pyrrolidone crosslinked	26 g
Sodium stearyl fumarate	1.4 g

Alginic acid, sodium hydrogencarbonate, microcrystalline cellulose, polyvinyl pyrrolidone and sodium stearyl fumarate were dry-mixed and precompressed as a first layer in a tableting machine equipped with 10x21 mm oval punches. Microcrystalline cellulose was filled on top of the first layer to form a separating layer to the next layer.

The enteric coating layered pellets, microcrystalline cellulose, polyvinyl pyrrolidone and sodium stearyl fumarate were dry-mixed and filled on top of the separating layer. The three layers were compressed into a three layers tablet.

Optionally the tablet was covered by a tablet coating layer.

The amount of omeprazole in each tablet is approx. 10 mg and the amount of alginic acid was approx 500 mg.

The best mode to practise the invention is described in Examples 1 and 4.

The enteric coating layered pellets comprising a proton pump inhibitor may also be prepared as described in the following examples.

Example 5

Preparation of enteric coating layered pellets by extrusion/spheronization.

Core material	
Magnesium omeprazole	600 g
Mannitol	1000 g
Microcrystalline cellulose	300 g
Hydroxypropyl cellulose	100 g
Sodium lauryl sulphate	6 g
Water purified	802 g
Separating layer	
Core material	400 g
Hydroxypropyl methylcellulose	48 g
Water purified	960 g
Enteric coating layer	
Pellets covered with separating layer	200 g
Methacrylic acid copolymer	100 g
Triethyl citrate	30 g
Mono- and diglycerides (NF)	5 g
Polysorbate 80	0.5 g
Water purified	309 g

Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid. Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.

The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

Example 6

Preparation of enteric coating layered pellets by powder layering of sugar sphere seeds.

Core material	
Magnesium omeprazole	1 500 g
Sugar sphere seeds	1 500 g
Hydroxypropyl methylcellulose	420 g
Aerosil®	8 g
Water purified	4 230 g
Separating layer	
Core material	500 g
Hydroxypropyl cellulose	40 g
Talc 67 g	
Magnesium stearate	6 g
Water purified	800 g
Enteric coating layer	
Pellets covered with separating layer	500 g
Methacrylic acid copolymer	200 g
Triethyl citrate	60 g
Water purified	392 g

Magnesium omeprazole, part of the hydroxypropyl methylcellulose and Aerosil® are dry-mixed forming a powder. Sugar sphere seeds (0.25-0.40 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).

The prepared core material is dried and covered by a separating layer in a centrifugal fluidized coating-granulator. A fluid bed apparatus is used for enteric coating layereing.

Example 7

Preparation of enteric coating layered pellets with cores of silicon dioxide seeds.

Core material	
Magnesium omeprazole	8.00 kg
Silicon dioxide	8.00 kg
Hydroxypropyl methylcellulose	1.41 kg
Sodium lauryl sulphate	0.08 kg
Water purified	28.00 kg
Separating layer	
Core material (acc. to above)	10.00 kg
Hydroxypropyl methylcellulose	0.80 kg
Water purified	10.00 kg
Enteric coating layer	
Pellets covered with separating layer (acc. to above)	300 g
Methacrylic acid copolymer	124 g
Polyethylene glycol 400	25 g
Mono- and diglycerides (NF)	3 g
Polysorbate 80	1 g

Water purified	463 g

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto the silicon dioxide seeds from a water suspension containing the dissolved binder and a surface active ingredient.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose solution. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, polyethylene glycol 400 and polysorbate is sprayed onto the pellets covered with separating layer in a fluid bed apparatus.

Example 8

Preparation of enteric coating layered pellets.

Enteric coating layer

Pellets covered with separating layer (manufacturing and composition as in example 10)	500 g
Methacrylic acid copolymer	250 g
Polyethylene glycol 6000	75 g
Mono- and diglycerides (NF)	12.5 g
Polysorbate 80	1.2 g
Water purified	490 g

Example 9

Preparation of enteric coating layered pellets.

Enteric coating	
Pellets covered with separating layer	500 g
(manufacturing and composition as in example 1)	
Hydroxypropyl methylcellulose phthalate	250 g
Cetanol	50 g
Ethanol (95%)	1000 g
Acetone	2500 g

Example 10

Preparation of enteric coating layered pellets.

Core material	
Omeprazole	225 g
Mannitol	1425 g
Hydroxypropyl cellulose	60 g
Microcrystalline cellulose	40 g
Lactose anhydrous	80 g
Sodium lauryl sulphate	5 g
Disodium hydrogen phosphate dihydrate	8 g
Water purified	350 g

Separating layer	
Core material	300 g
Hydroxypropyl cellulose	30 g
Talc	51 g
Magnesium stearate	4 g

Enteric coating layer	
Pellets covered with separating layer	300 g

Methacrylic acid copolymer	140 g
Triethyl citrate	42 g
Mono- and diglycerides (NF)	7 g
Polysorbate 80	0.7 g

The dry ingredients for producing the core material are well mixed in a mixer. Addition of granulation liquid is made and the mixture is kneeded and granulated to a proper consistency. The wet mass is pressed through an extruder screen and the granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed apparatus and classified into a suitable particle size range, e.g. 0.5 - 1.0 mm.The prepared core material is covered with a separating layer and enteric coating layered as described in previous examples.

Preparation of active substance.

Magnesium omeprazole used in some of the examples is produced according to the process described in WO95/01977, the single enantiomers of omeprazole salts are prepared as described in WO94/27988 and omeprazole is produced according to the process disclosed in EP-A1 0005129. These documents are hereby incorporated in a whole by reference.

CLAIMS

1. An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor together with one or more antacid agents or alginates and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of a fixed unit dosage form comprising at least two pharmaceutically active components and wherein the proton pump inhibitor is protected by an enteric coating layer.

2. A dosage form according to claim 1, wherein the dosage form is a tablet formulation.

3. A dosage form according to claim 1, wherein the dosage form is a sachet formulation.

4. A dosage form according to claim 1, wherein the proton pump inhibitor is protected by two layers, an enteric coating layer and a layer separating the enteric coating from the proton pump inhibitor.

5. A dosage form according to claim 1, wherein the dosage form comprises an acid susceptible proton pump inhibitor and two antacid agents.

6. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole, one of its single enantiomers or an alkaline salt thereof.

7. A dosage form according to claim 6, wherein the proton pump inhibitor is (s)-omeprazole magnesium salt.

8. A dosage form according to claim 1, wherein the proton pump inhibitor is lansoprazole, one of its single enantiomers or an alkaline salt thereof.

9. A dosage form according to one of claims 6 - 8, wherein the antacid agents are aluminium hydroxide in combination with magnesium carbonate.

10. A dosage form according to any of claims 6 - 8, wherein the antacid agents are magnesium hydroxide in combination with calcium carbonate.

11. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 5-80 mg and the amount of antacid/alginate is in the range of 100-900 mg.

12. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-40 mg and the amount of antacid/alginate is in the range of 250-650 mg.

13. A tableted dosage form according to claim 2, wherein the dosage form consists of two separate layers optionally separated by a separating layer, and one layer comprising a proton pump inhibitor and the other layer comprising one or more antacid agents or alginates.

14. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising the acid susceptible proton pump inhibitor in the form of enteric coating layered pellets compressed together with a antacid preparation into a tablet, whereby the enteric coating layer covering the individual pellets has mechanical properties such that the tableting of the pellets together with the antacid preparation and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the enteric coating layered pellets.

15. A tableted dosage form according to claim 14, wherein the acid resistance of the enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopeia.

16. A tableted dosage form according to claim 14, wherein the acid resistance of the enteric coating layered pellets does not decrease more than 10 % during the compression of the pellets into the multiple unit tableted dosage form.

17. A tableted dosage form according to claim 14, wherein the enteric coating of the pellets comprises a plasticized enteric coating layer material.

18. A tableted dosage form according to claim 14, wherein the enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.

19. A tableted dosage form according to claim 14, wherein the tablet is divisible.

20. A tableted dosage form according to claim 19, wherein the tablet is dispersible to an aqueous suspension comprising antacid agent(s) and enteric coating layered pellets of a proton pump inhibitor.

21. A tableted dosage form according to claim 2, wherein the tablet is an enteric coating layered tablet comprising the proton pump inhibitor surrounded by a layer comprising the antacid preparation.

22. A tableted dosage form according to claim 14, wherein the proton pump inhibitor is in the form of a multiple unit tableted dosage form surrounded with a separate layer comprising the antacid agent(s) or an alginate preparation.

23. A process for the manufacture of a fixed dosage form comprising an acid susceptible proton pump inhibitor in one layer and one or more antacid agents or an alginate in another layer, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets, the pellets are mixed with pharmaceutically acceptable excipients

and precompressed and further layered with a surrounding layer of an antacid or an alginate preparation and finally compressed into a tablet.

24. A process for the manufacture of a fixed dosage form comprising an acid susceptible proton pump inhibitor and one or more antacid agents in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with an antacid preparation and optionally pharmaceutically acceptable tablets excipients whereafter the dry mixture is compressed into a multiple unit tablet without giving any significant change of the acid resistance of the enteric coating layer.

25. A process for the manufacture of a fixed dosage form comprising an acid susceptible proton pump inhibitor and one or more antacid agent(s) in an enteric coating layered tablet characterized in that the proton pump inhibitor is admixed with tablet excipients and compressed into a tablet, which tablet is covered with an enteric coating layer and optionally a separating layer has applied onto the tablet before the enteric coating layer, the antacid agent(s) mixed with pharmaceutically acceptable excipients are thereafter compressed onto the enteric coating layered tablet.

26. A method for the treatment of disorders associated with dyspepsia in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 22.

27. A method according to claim 26, wherein the disorder is a gastric disorder associated with heartburn.

28. Use of a dosage form according to any of claims 1 to 22 for the manufacture of a medicament for the treatment of disorders associated with dyspepsia.

29. Use according to claim 28, wherein the disorder is a gastric disorder associated with heartburn.

Fig. 1

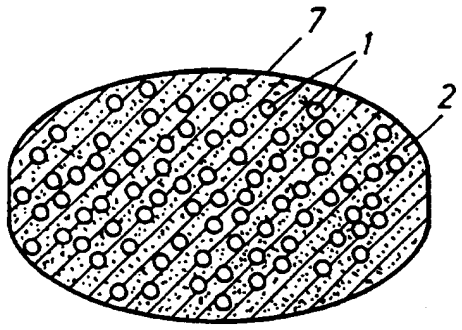


Fig. 2

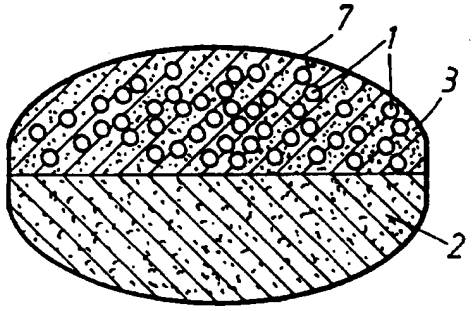
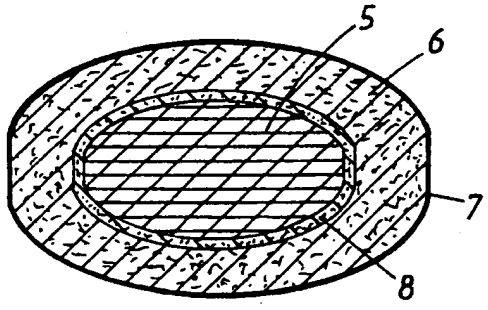


Fig. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01737

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 45/06, A61K 31/44, A61K 33/08, A61K 33/10, A61K 9/20, A61K 9/26
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, WPI, WPIL, CLAIMS, CA PLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0338861 A2 (WALTON S.A.), 25 October 1989 (25.10.89), column 1, line 52 - column 2, line 14; column 2, line 15 - line 22; column 3, line 52 - line 57, figures 7-8 --	1-29
X	US 5244670 A (J.G. UPSON ET AL), 14 Sept 1993 (14.09.93), column 1, line 59 - line 68; column 2, line 43 - line 55 --	1-29
A	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87), page 4, line 25 - page 5, line 2; page 8, line 22 - line 32 --	14-29

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 1997	22 -04- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01737

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90), page 3, line 41 - line 46; page 4, line 42 - line 57 --	14-29
A	STN International, File CAPLUS, CAPLUS accession no. 1989:490176, K. Takeuchi et al: "Healing process of duodenal ulcers induced by indomethacin plus histamine in rats", Digestion (1989), 42(4), 202-11 -- --------	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01737

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 26-27
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Claims 26-27 are directed to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.
PCT/SE 96/01737

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INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.
PCT/SE 96/01737

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